Experimental Use of Testosterone Compounds in Premature Infants

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PREVIOUS laboratory investigations have indicated that the premature infant has many metabolic defects. In particular there are inadequacies in nitrogen, calcium, and phosphorus storage; faulty ability to absorb fat; and multiple requisites conditioned by the rapid rate of growth. Since nitrogen storage and utilization are in part the physiological effects desired, it occurred to us that testosterone, one of the most important metabolizers of nitrogen, might be a rational drug to employ as an adjunct in the care of certain premature infants.[3]

During the past year infants of both sexes on the premature wards of the Los Angeles County General Hospital received various testosterone compounds and the effects were observed. The materials considered suitable for such a study were the methyl derivatives for oral use, and the propionate derivatives for intramuscular administration. Methyl testosterone is obtainable in tablet form which can be crushed and introduced directly into the formula, or as a propylene glycol solution which may be dropped directly under the tongue. Without precedent the dose of methyl testosterone was arbitrarily set at 5 mg. daily. It was found that the propylene glycol solution lent itself more readily to administration. Testosterone propionate was given intramuscularly in 4 mg. doses daily. Treatment in both series was begun at 12 hours after birth and continued for three weeks.

The infants observed weighed under 2000 grams and for each group there was a similar group of the same age and weight, under the same general care, as control. Daily observations were made of the weight, alertness, type of stool, amount of lanugo, size of clitoris and penis, and the number of erections. These, in addition to the length of time required to regain the birth weight, and that required to gain to 2500 grams in body weight were used as the ultimate basis for evaluation.

To date there has been a total of 74 patients which have been under observation for a year. These infants, of both sexes, to which both types of testosterone compounds were given, have been divided into two groups, those weighing between 1000 and 1500 grams and those between 1500 and 2000 grams at birth. A significant indication of the benefits obtained by the use of both testosterone compounds was evident by the enhanced welfare of the treated prematures in both weight classifications. In the 1000 to 1500 gram weight groups an average of 14.7 days was required by the untreated controls to regain their birth weight. Those on methyl testosterone in the same weight group required an average of 9.0 days; and those on testosterone propionate only 7.5 days. Thus comparison between the treated and the control group reveals a 50 per cent reduction in the time required to regain birth weight. Similar results were obtained in the 1500 to 2000 gram group. It was also found that whereas the controls required 42 days to gain to 2500 grams, those to whom the propionate was administered required only 35 days and those receiving the methyl compound only 32 days to reach this same level. Again these treated prematures revealed a significantly earlier attainment of maturity when compared with their untreated controls.

An even better indication of the benefits derived from the use of testosterone compounds was obtained from the study of four sets of twins. Here the larger of the two, the one with the greater chance for survival, was used as the control while the smaller was given testosterone. All of the twins on the testosterone compounds, who theoretically should have taken longer to regain their birth weight, did so in a much shorter period than their larger more mature control siblings. In fact, in three of the four sets, the birth weight was maintained from the onset of treatment while in the fourth there was an approximate 50 per cent reduction in the anticipated number of days required to regain the birth weight. Here again the days required to gain to 2500 grams showed a reduction in the twin treated with testosterone in three out of the four, while in the fourth set only two days longer was required to bring the smaller infant to maturity.

It is now generally accepted that testosterone compounds cause a decline in urinary nitrogen reflected in the urea fraction, unaccompanied by an increase in the plasma protein, non-protein nitrogen, or hemoglobin concentrations.[1] As there is no change in the amount of fecal nitrogen, it is evident that this retention of nitrogen must have some tissue-building significance. There is also a decline in urinary sodium, associated with a somewhat smaller decline in urinary chloride, a decline in urinary potassium and in total urinary volume. The evident end result of this is in water retention and a general protein anabolism, noticeable in the genital tissue, but more objectivized in the soma, with resultant increased growth and muscle hypertrophy.

In other clinical experiments it has been found that testosterone propionate and methyl testosterone exercised similar effects.[5] The only exception appeared to be that some observers found that methyl testos-

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terone tended to promote hypercreatinuria whereas propionate decreased it.[4] It is now felt that the fundamental effects are the same. The apparent discrepancy in creatine metabolism is merely ascribable to the fact that in the case of methyl testosterone administration the nitrogen retention is so profound as to cause a spilling over of creatine. In comparing the clinical effects of methyl testosterone with the testosterone propionate, no significant differences could be observed in the prematures in our series. The intramuscular administration perhaps did offer advantages over the oral route in accuracy of dosage, but the ease of administration of methyl testosterone in propylene glycol and the freedom from the infection hazard are perhaps more worthy of consideration.

Daily observations for any of the previously mentioned signs of virilism revealed no significant difference between the groups. Our follow-up examinations during the first year continued to support these findings. Following prolonged and injudicious treatment with testosterone in some adolescent and adult females a lowering of the voice has been found.[2] We watched for such an untoward effect in the infants both during the administration period and throughout the first year following treatment but no abnormalities in cry could be detected. Roentgenograms of the long bones were taken at the beginning of the series and repeated at the end of the year. There was no difference in bone age between the controls and the treated infants, but in general all infants showed that slight delay in osseous development characteristic of prematures.

SUMMARY

Seventy-four premature infants, of both sexes, weighing under 2000 grams at birth were given either oral methyl testosterone 5 mg. daily, or testosterone propionate 4 mg. daily parenterally. A similar untreated group was observed as controls. A distinct shortening in the time required to regain birth weight and in the time required to gain to 2500 grams was noted in both treated groups. In four sets of twins the smaller, treated infant showed increased somatic development over its larger untreated control sibling. No contraindications to the use of testosterone compounds were observed.

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QUESTIONS AND ANSWERS

Question: What about mortality rates of treated and untreated prematures?

DR. MARK: In our preliminary series we have not found any statistically significant differences between the mortality rates of the treated and the untreated premature infants. This is understandable as our treatment was begun at the end of 24 hours and it is during this time that the greatest mortality occurs in premature infants. However, Varden, who has done similar work in a San Bernardino hospital with premature infants, reports a lower mortality rate in those individuals treated.

Question: Regarding testosterone, and the interval you use—three weeks—have you any information on other intervals that might be used, and any information on catheterizations or prolonged administration?

DR. MARK: In this, the first series we have ever attempted, three weeks was chosen arbitrarily. It was believed that during this time a maximum physiological effect could be obtained with no possibility of any adverse effects due to prolonged treatment. Our follow-up study at the end of the first year supports this view. Experimental work shows that up to eight months of treatment with high doses has no effect on the epiphyseal centers.